



Modelling cardiac electrophysiology with structural heterogeneities and dynamical gap junctions

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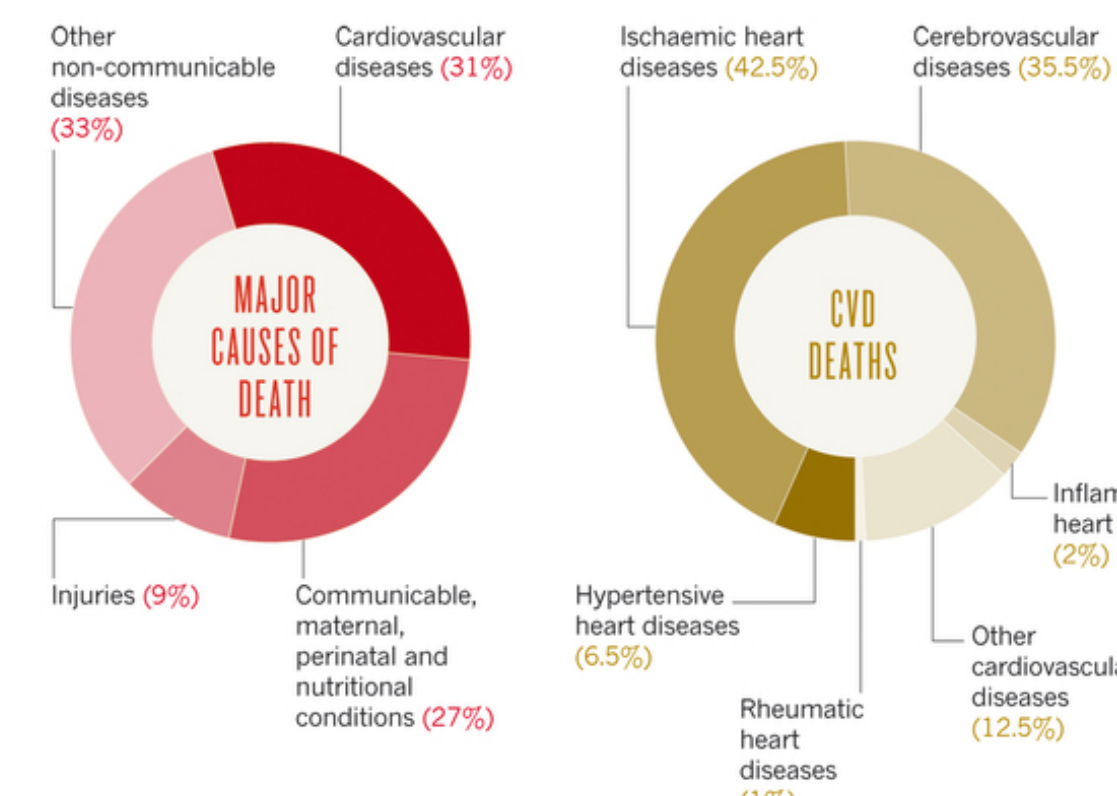
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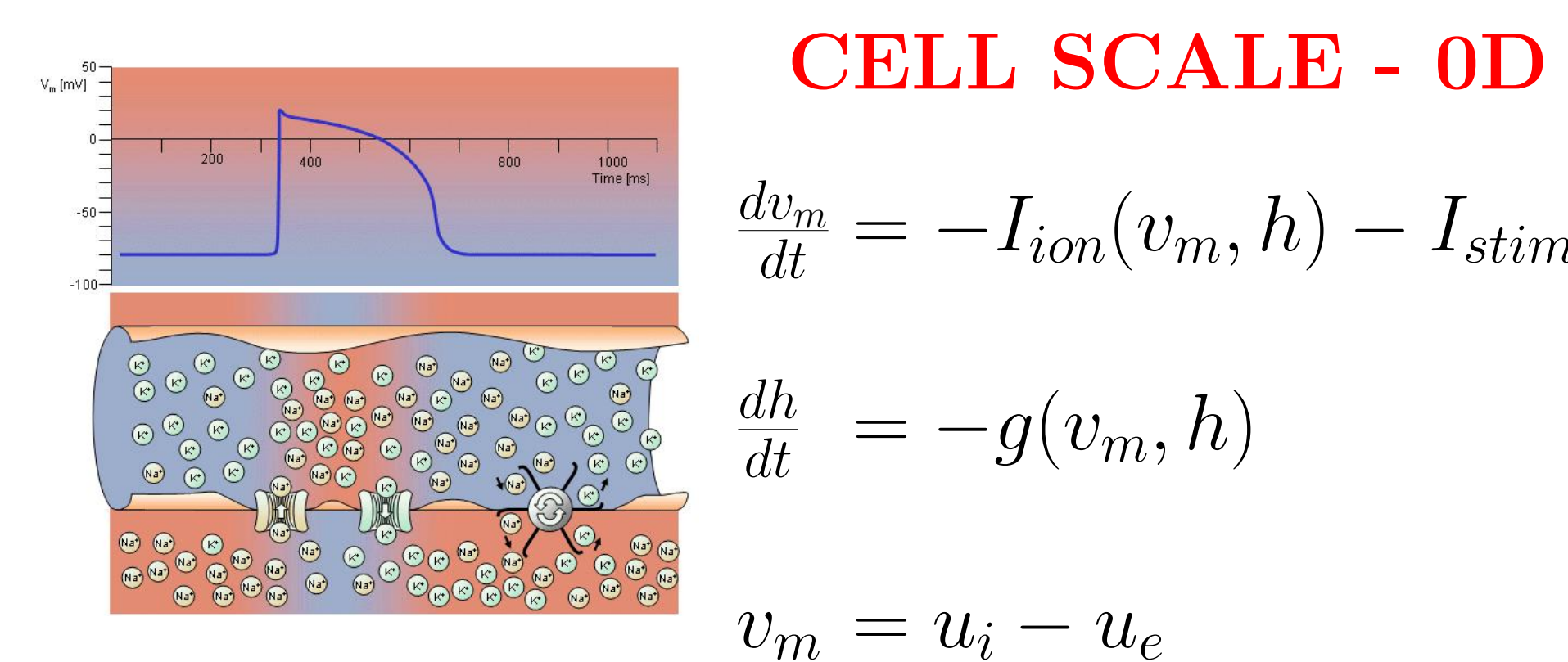
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Why?

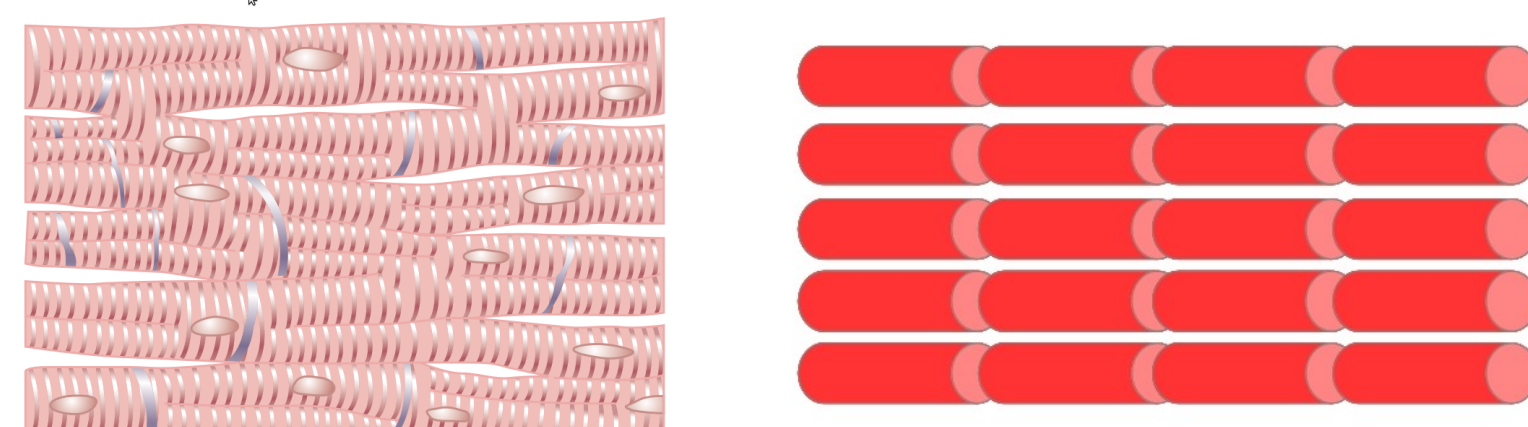


- > 17 000 000 people die every year
- medical care - millions of EUR

Multiscale Modelling



TISSUE SCALE - 2D or 3D



- Bidomain model (Neu-Krassowska, 1993)

$$\begin{aligned} \partial_t h + g(v_m, h) &= 0 \\ \partial_t v_m + I_{ion}(v_m, h) &= \nabla \cdot (\sigma^i \nabla u^i) \\ \partial_t v_m + I_{ion}(v_m, h) &= -\nabla \cdot (\sigma^e \nabla u^e) \end{aligned}$$

- generalised cable equation
- derived from microscopic equations
- anisotropic model

SCARS - BLACK BOXES

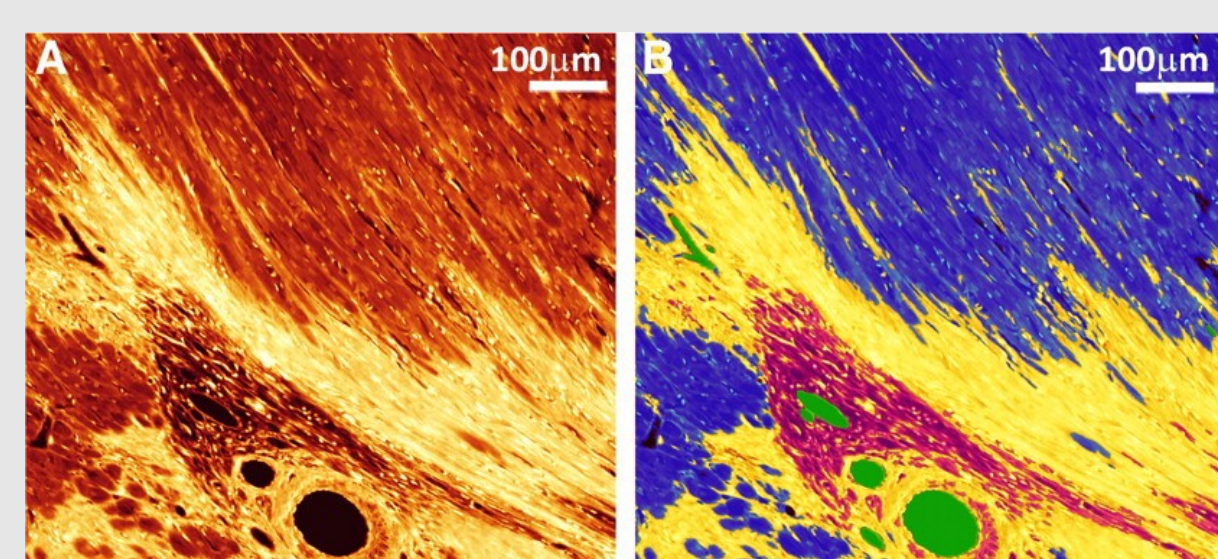


Figure : The infarct border zone. (Rutherford, 2012)

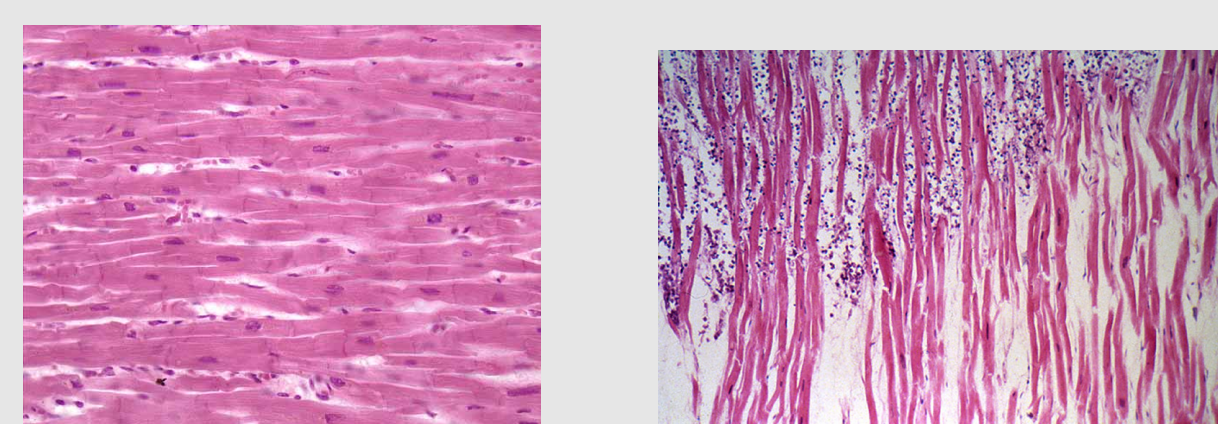


Figure : Normal vs myocardial infarction in human.

MAIN FACTORS

- Nonlinear ionic currents
- **MICROSTRUCTURE**
- Gap Junctions (resistors?)

Assumptions

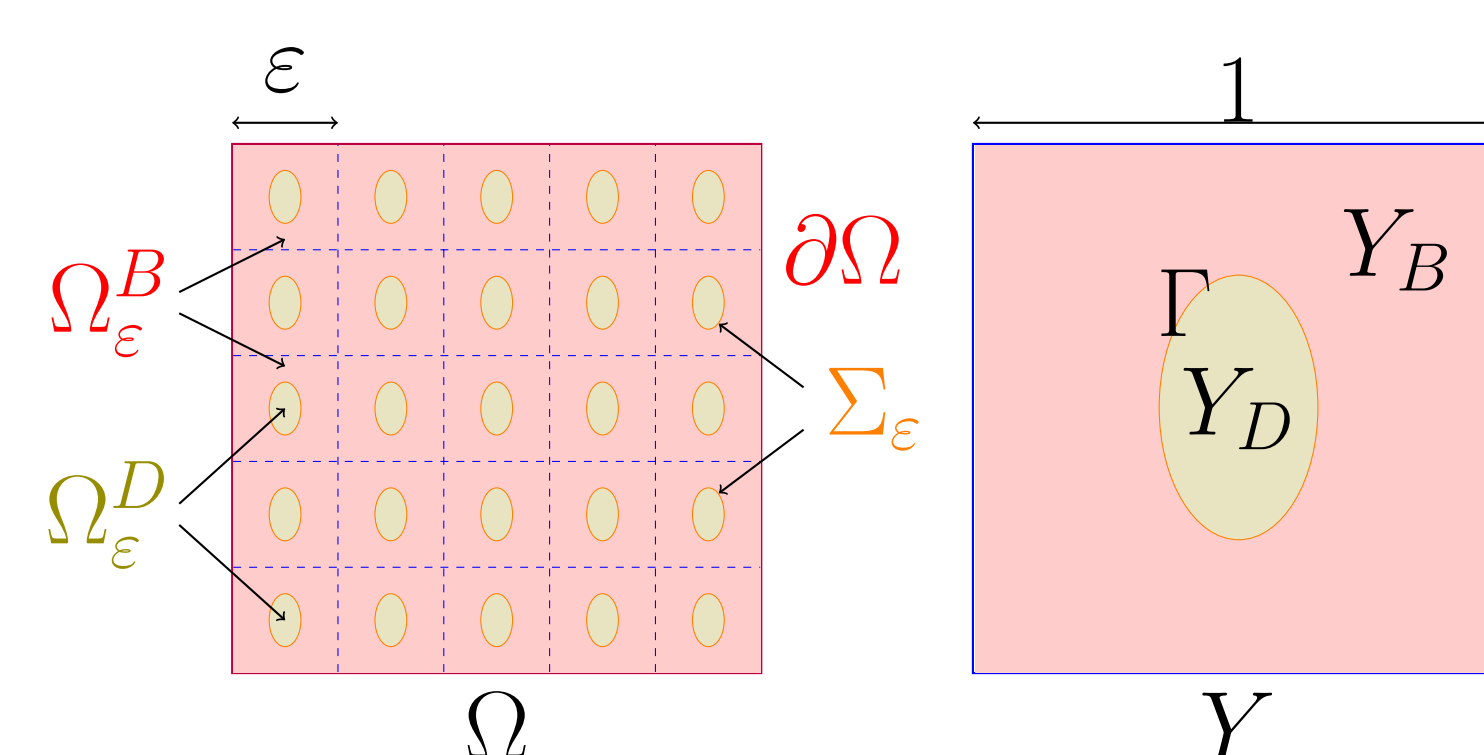
- **Periodic** inclusions of size ε .
- Isotropic conductivity in the inclusions.
- No cells in the inclusions - **passive conductors**.
- Standard transmission conditions.

MESOSCALE MODEL

$$\begin{aligned} \partial_t h_\varepsilon + g(v_\varepsilon, h_\varepsilon) &= 0, & \text{in } \Omega_\varepsilon^B, \\ \partial_t v_\varepsilon + I_{ion}(v_\varepsilon, h_\varepsilon) &= \nabla \cdot (\sigma_\varepsilon^i \nabla u_\varepsilon^i), & \text{in } \Omega_\varepsilon^B, \\ \partial_t v_\varepsilon + I_{ion}(v_\varepsilon, h_\varepsilon) &= -\nabla \cdot (\sigma_\varepsilon^e \nabla u_\varepsilon^e), & \text{in } \Omega_\varepsilon^B. \end{aligned}$$

$$\nabla \cdot (\sigma_\varepsilon^d \nabla u_\varepsilon^d) = 0, \quad \text{in } \Omega_\varepsilon^D.$$

$$\left. \begin{aligned} \sigma_\varepsilon^i \nabla u_\varepsilon^i \cdot \mathbf{n}_{\Sigma_\varepsilon} &= 0, \\ \sigma_\varepsilon^e \nabla u_\varepsilon^e \cdot \mathbf{n}_{\Sigma_\varepsilon} &= \sigma_\varepsilon^d \nabla u_\varepsilon^d \cdot \mathbf{n}_{\Sigma_\varepsilon}, \\ u_\varepsilon^e &= u_\varepsilon^d, \end{aligned} \right\} \quad \text{on } \Sigma_\varepsilon.$$



MODIFIED BIDOMAIN MODEL

- Limit macroscale model

$$\begin{aligned} \partial_t h_0 + g(v_0, h_0) &= 0, \\ |Y_B|(\partial_t v_0 + I_{ion}(v_0, h_0)) &= \nabla \cdot (\tilde{\sigma}_i \nabla u_0^i), \\ |Y_B|(\partial_t v_0 + I_{ion}(v_0, h_0)) &= -\nabla \cdot (\tilde{\sigma}_e \nabla u_0^e). \end{aligned}$$

$$\begin{aligned} \tilde{\sigma}_i &= \sigma^i |Y_B| + A^i(\sigma_i, w^i), \\ \tilde{\sigma}_e &= \sigma^e |Y_B| + \sigma^d |Y_D| + A(\sigma_e, \sigma_d, w) \end{aligned}$$

- **UPDATED CONDUCTIVITIES!**
- A_i , A matrices obtained by solving the cell problems on Y for w^i and w .
- volume fraction AND geometry

A word on homogenisation..

- **Full problem depends on $\varepsilon \Rightarrow$ very expensive**
- Averaging solution:
Let $\varepsilon \rightarrow 0$

$$L_\varepsilon u_\varepsilon = f \rightarrow Lu = f$$

- Formal asymptotic expansion

$$u_\varepsilon(t, x) = u_0(t, x, x/\varepsilon) + \varepsilon u_1(t, x, x/\varepsilon) + \dots$$

\Rightarrow Cascade PDE systems

- **Cell problems** for new variables w - define dependence of u_1 on u_0 - solved once.
- **Homogenised problem** - limit macroscale problem on u_0 that does not depend on ε .
- **A priori estimates** ensure two scale convergence (Allaire, 1992)
- Difficulty - **nonlinear** ionic functions

Numerical results

- *FreeFem++* and *gnuplot*
- Mitchell Schaeffer ionic model
- 2D simulations on rectangle, SBDF2 scheme
- Circular and elliptical inclusions

Table : Modified conductivities. C - circles, E - ellipses.

| Inclusions | Vol. fraction | σ_{i11}^* | σ_{i22}^* | σ_{e11}^* | σ_{e22}^* |
|------------|---------------|------------------|------------------|------------------|------------------|
| none | 0.0 | 1.74 | 0.19 | 3.9 | 1.97 |
| C | 0.18 | 1.29 | 0.18 | 3.28 | 2.45 |
| C | 0.2 | 1.26 | 0.17 | 3.29 | 2.53 |
| C | 0.4 | 1.07 | 0.15 | 3.42 | 3.53 |
| C | 0.7 | 0.69 | 0.09 | 5.08 | 7.89 |
| E - long | 0.18 | 0.31 | 0.19 | 0.75 | 2.61 |
| E - short | 0.2 | 1.13 | 0.18 | 2.82 | 2.58 |
| E - medium | 0.2 | 0.86 | 0.18 | 2.09 | 2.64 |
| E - short | 0.4 | 0.81 | 0.16 | 2.53 | 3.70 |

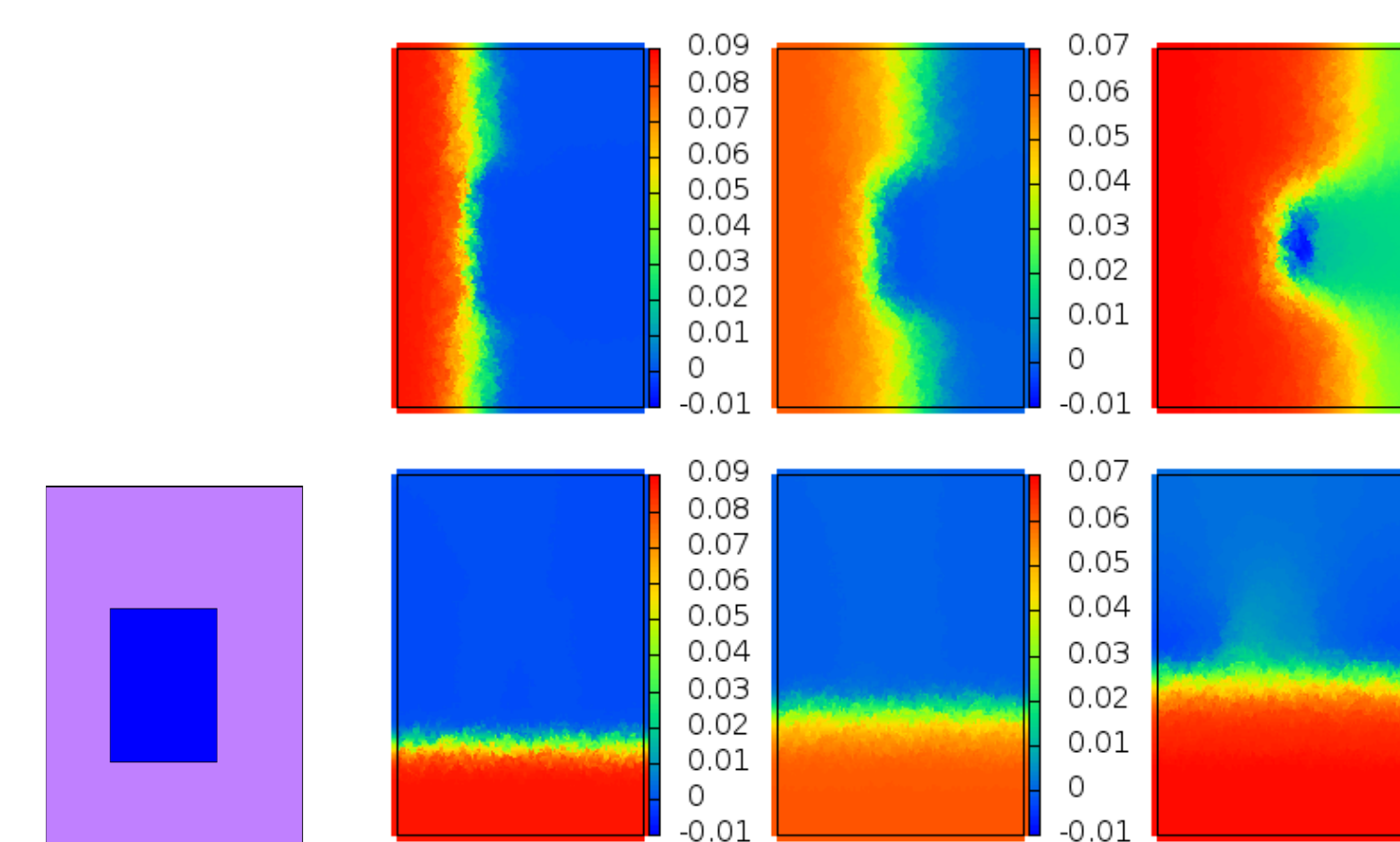


Figure : Propagation of v_m in heterogeneous tissue.

What about GAP JUNCTIONS?

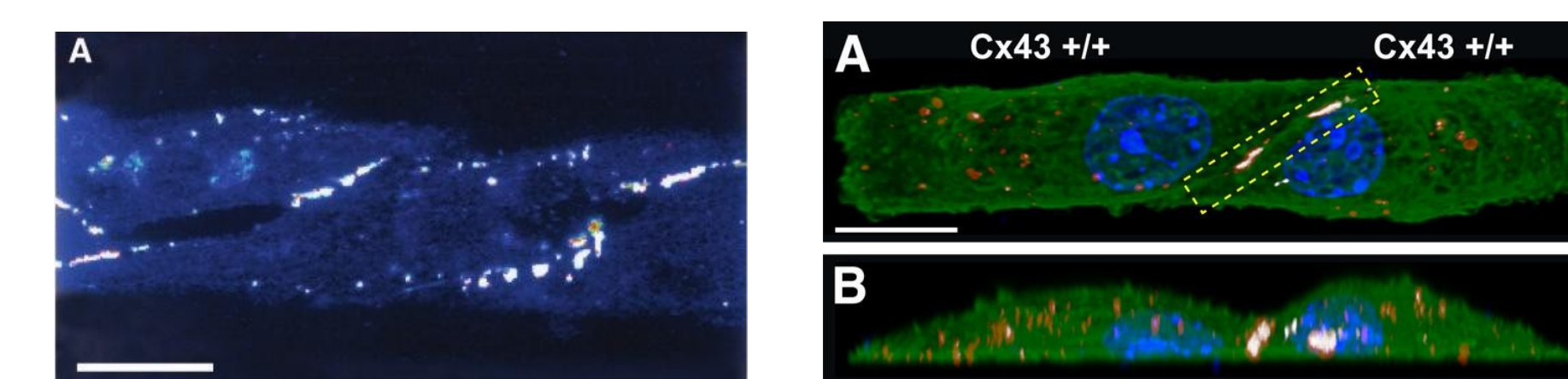


Figure : Immunohistochemical analysis of Cx43.
Left: Bar = $10\mu m$. (Beauchamp, 2004) Right: top view(A), lateral view(B). Bar = $5\mu m$. (Beauchamp, 2012)

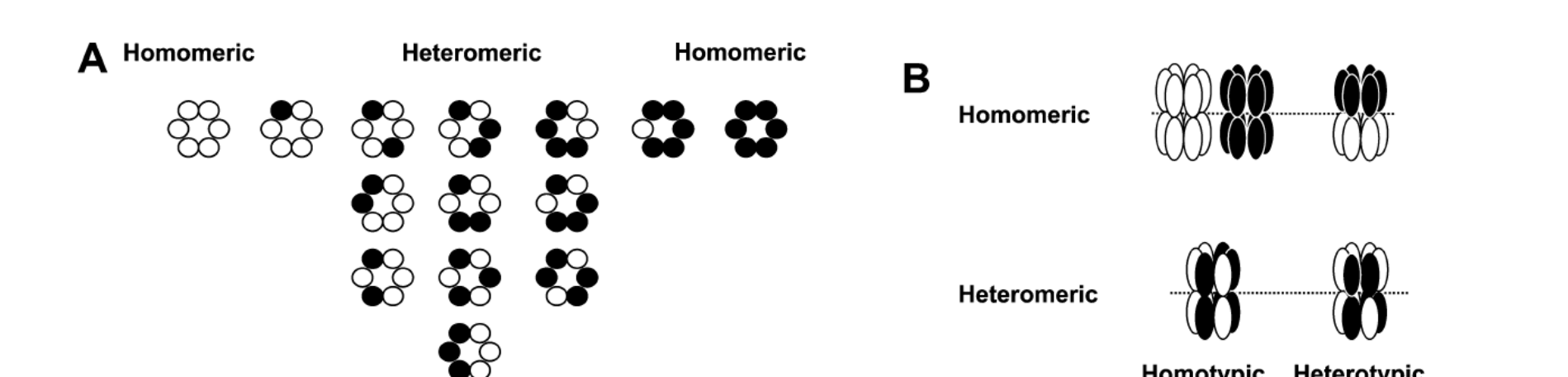


Figure : Predicted configurations of connexons and gap junction channels for two different connexins. (Desplantez, 2004)

- Distributed around the cell perimeters.
- Expressed in ventricles: Cx43, Cx45 and Cx40.
- In recent models:

$$I_j = g_j V_j$$

with $g_j = \text{const}$ and V_j - transjunctional voltage.

NON LINEAR MODEL

- Gating variable: $g_j = g_j(t, V_j)$
 $\frac{dg_j}{dt} = \frac{g_\infty(V_j) - g_j}{\tau_\infty(V_j)}$
- Fit experimental data to find g_∞/g_0 and τ_∞ .

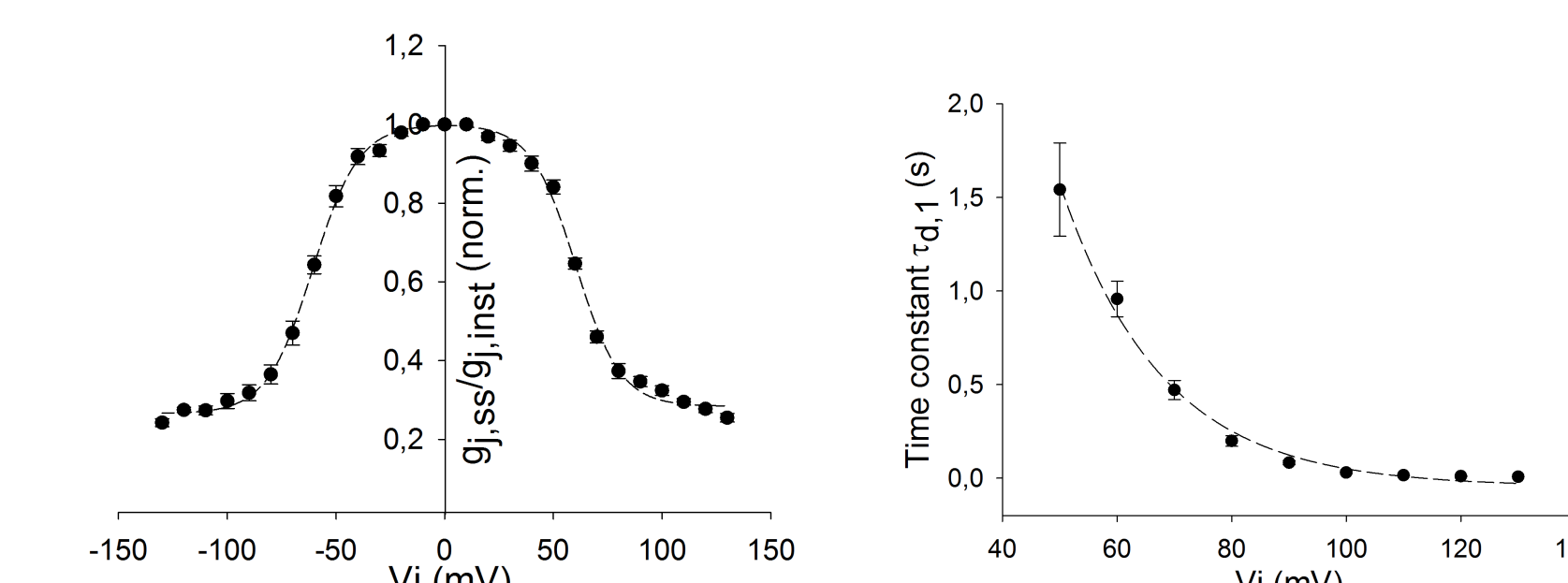


Figure : Fitting the non-linear model to the experimental data for the homomeric Cx43 gap junction in rodent.

$$g_j = g_\infty + (g_0 - g_\infty)e^{-\frac{t}{\tau_\infty}}$$

Work in progress... and beyond

- Current work: including GJ model
 - (i) as boundary condition
 - (ii) rescaling propagation front
- Future work:
 - SCAR modelling
 - Late enhancement MRI